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DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. 00D–0084]

Draft Guidance for Industry on Special Protocol Assessment; Availability

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA) is announcing the availability of a draft guidance for industry entitled ''Special Protocol Assessment.'' This draft guidance is intended to provide guidance for industry on procedures that will be adopted by the Center for Drug Evaluation and Research (CDER) and the Center for Biologics Evaluation and Research (CBER) to evaluate issues related to the adequacy (e.g., design, conduct, analysis) of certain proposed studies.

DATES: Submit written comments on the draft guidance and the collection of information provisions by [*insert date 60 days after date of publication in* **Federal Register**]. General comments on agency guidance documents are welcome at any time.

ADDRESSES: Copies of this draft guidance for industry are available on the Internet at http:// www.fda.gov/cder/guidance/index.htm or http://www.fda.gov/cber/guidelines.htm. Submit written requests for single copies of the draft guidance to the Drug Information Branch (HFD–210), Center for Drug Evaluation and Research, Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857; or the Office of Communication, Training, and Manufacturers Assistance (HFM–40), Center for Biologics Evaluation and Research, 1401 Rockville Pike, Rockville, MD 20852–1448, 301–827–3844, FAX: 888–CBERFAX. Send two self-addressed adhesive labels to assist the office in processing your requests. Submit written comments to the Dockets Management Branch (HFA–305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. Requests

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and comments should be identified with the docket number found in brackets in the heading of this document.

FOR FURTHER INFORMATION CONTACT: Murray M. Lumpkin, Center for Drug Evaluation and Research (HFD–2), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301–594–5400; or Robert A. Yetter, Center for Biologics Evaluation and Research (HFM–10), Food and Drug Administration, 1401 Rockville Pike, Rockville, MD 20852–1448, 301–827–0373.

SUPPLEMENTARY INFORMATION:

I. Description of the Guidance

FDA is announcing the availability of a draft guidance for industry entitled ''Special Protocol Assessment.'' The draft guidance is intended to provide guidance for industry on procedures that will be adopted by CDER and CBER to evaluate issues related to the adequacy (e.g., design, conduct, analysis) of certain proposed studies. This draft guidance describes procedures for sponsors to request special protocol assessment and for the agency to act on such requests.

The Prescription Drug User Fee Act of 1992 (PDUFA) (Public Law 102–571) was reauthorized in November 1997 as part of the Food and Drug Administration Modernization Act of 1997 (the Modernization Act) (Public Law 105–115). In conjunction with the reauthorization of PDUFA, FDA agreed to specific performance goals (PDUFA goals) for activities associated with the development and review of products in human drug applications as described in section 735(1) of the Federal Food, Drug, and Cosmetic Act (the act) (21 U.S.C. 379g) (PDUFA products). The PDUFA goals are summarized in ''PDUFA Reauthorization Performance Goals and Procedures,'' an enclosure to a letter dated November 12, 1997, from the Secretary of the U.S. Department of Health and Human Services, Donna E. Shalala, to Senator James M. Jeffords. The PDUFA goals for special protocol assessment and agreement provide that, upon request by a sponsor, FDA will evaluate within 45 days of receipt certain protocols and issues relating to the protocols to assess whether their design is adequate to meet scientific and regulatory requirements identified by the sponsor. Three types of protocols are eligible for this special protocol assessment under

the PDUFA goals: (1) Animal carcinogenicity protocols, (2) final product stability protocols, and (3) clinical protocols for phase 3 trials whose data will form the primary basis for an efficacy claim if the trials had been the subject of discussion at an end-of-phase 2/pre-phase 3 meeting with the review division or if the division is otherwise aware of the developmental context in which the protocol is being reviewed and the questions are being answered. These protocols for phase 3 clinical trials may relate to efficacy claims that will be part of an original new drug application (NDA) or biologics license application (BLA) or that will be part of an efficacy supplement to an approved NDA or BLA.

Section 119(a) of the Modernization Act amends section 505(b) of the act (21 U.S.C. 355(b)). Section 505(b)(4)(B) of the act directs FDA to meet with sponsors and applicants, provided certain conditions are met, for the purpose of reaching agreement on the design and size of clinical trials intended to form the primary basis of an effectiveness claim in a marketing application submitted under section 505(b) of the act or section 351 of the Public Health Service Act (42 U.S.C. 262) (the PHS Act). Such marketing applications include NDA's, BLA's, and efficacy supplements to approved NDA's and BLA's.

The procedures and policies described in this draft guidance are designed to implement section 505(b)(4)(B) of the act and the PDUFA goals for special protocol assessment and agreement.

This draft Level 1 guidance is being issued consistent with FDA's good guidance practices (62 FR 8961, February 27, 1997). The draft guidance represents the agency's current thinking on special protocol assessment in CDER and CBER. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statute, regulations, or both.

Interested persons may submit to the Dockets Management Branch (address above) written comments on the draft guidance. Two copies of any comments are to be submitted, except that individuals may submit one copy. Comments should be identified with the docket number found in brackets in the heading of this document. The draft guidance and received comments are

available for public examination in the Dockets Management Branch between 9 a.m. and 4 p.m., Monday through Friday.

II. The Paperwork Reduction Act of 1995

Under the Paperwork Reduction Act of 1995 (the PRA) (44 U.S.C. 3501–3520), Federal agencies must obtain approval from the Office of Management and Budget (OMB) for each collection of information they conduct or sponsor. ''Collection of information'' is defined in 44 U.S.C. 3502(3) and 5 CFR 1320.3(c) and includes agency requests or requirements that members of the public submit reports, keep records, or provide information to a third party. Section 3506(c)(2)(A) of the PRA (44 U.S.C. 3506(c)(2)(A)) requires Federal agencies to provide a 60-day notice in the **Federal Register** concerning each proposed collection of information before submitting the collection to OMB for approval. To comply with this requirement, FDA is publishing notice of the proposed collection of information set forth in this document.

With respect to the following collection of information, FDA invites comment on: (1) Whether the proposed collection of information is necessary for the proper performance of FDA's functions, including whether the information will have practical utility; (2) the accuracy of FDA's estimate of the burden of the proposed collection of information, including the validity of the methodology and assumptions used; (3) ways to enhance the quality, utility, and clarity of the information to be collected; and (4) ways to minimize the burden of the collection on respondents, including through the use of automated collection techniques, when appropriate, and other forms of information technology.

Title: Draft Guidance for Industry on Special Protocol Assessment

Description: FDA is issuing a draft guidance on agency procedures to evaluate issues related to the adequacy of certain proposed studies. The draft guidance describes procedures for sponsors to request special protocol assessment and for the agency to act on such requests. The draft guidance provides information on how the agency will interpret and apply provisions of the Modernization

Act and the specific PDUFA goals for special protocol assessment associated with the development and review of PDUFA products.

The draft guidance describes two collections of information: (1) The submission of a notice of intent to request special protocol assessment of a carcinogenicity protocol, and (2) the submission of a request for special protocol assessment.

A. Notification for a Carcinogenicity Protocol

As described in the draft guidance, a sponsor interested in agency assessment of a carcinogenicity protocol should notify the appropriate division in CDER or CBER of an intent to request special protocol assessment at least 30 days prior to submitting the request. With such notification, the sponsor should submit relevant background information so that the agency may review reference material related to carcinogenicity protocol design prior to receiving the carcinogenicity protocol. The agency is currently drafting a separate guidance describing the type of information that would be appropriate to submit before requesting carcinogenicity protocol assessment.

B. Request for Special Protocol Assessment

In the draft guidance, CDER and CBER ask that a request for special protocol assessment be submitted as an amendment to the investigational new drug application (IND) for the underlying product and that it be submitted to the agency in triplicate with Form FDA 1571 attached. The agency also suggests that the sponsor submit the cover letter to a request for special protocol assessment via facsimile to the appropriate division in CDER or CBER. Agency regulations (21 CFR 312.23(d)) state that information provided to the agency as part of an IND is to be submitted in triplicate and with the appropriate cover form, Form FDA 1571. An IND is submitted to FDA under existing regulations in part 312 (21 CFR part 312), which specifies the information that manufacturers must submit so that FDA may properly evaluate the safety and effectiveness of investigational drugs and biological products. The information collection requirements resulting

from the preparation and submission of an IND under part 312 have been estimated by FDA and the reporting and recordkeeping burden has been approved by OMB until December 31, 1999, under OMB control number 0910–0014. In the **Federal Register** of May 6, 1999 (64 FR 24402), FDA published a notice requesting comments on the burden estimates for the information collection requirements in part 312. The notice also requested an extension of OMB approval for this information collection.

FDA suggests that the cover letter to the request for special protocol assessment be submitted via facsimile to the appropriate division in CDER or CBER to enable agency staff to prepare for the arrival of the protocol for assessment. The agency recommends that a request for special protocol assessment be submitted as an amendment to an IND for two reasons: (1) To ensure that each request is kept in the administrative file with the entire IND, and (2) to ensure that pertinent information about the request is entered into the appropriate tracking data bases. Use of the information in the agency's tracking data bases enables the appropriate agency official to monitor progress on the evaluation of the protocol and to ensure that appropriate steps will be taken in a timely manner.

CDER and CBER have determined and the draft guidance recommends that the following information should be submitted to the appropriate Center with each request for special protocol assessment so that the Center may quickly and efficiently respond to the request:

1. Questions to the agency concerning specific issues regarding the protocol; and

2. All data, assumptions, and information needed to permit an adequate evaluation of the protocol, including: (1) The role of the study in the overall development of the drug; (2) information supporting the proposed trial, including power calculations, the choice of study endpoints, and other critical design features; (3) regulatory outcomes that could be supported by the results of the study; (4) final labeling that could be supported by the results of the study; and (5) for a stability protocol, product characterization and relevant manufacturing data.

1. Description of Respondents

A sponsor, applicant, or manufacturer of a drug or biologic product regulated by the agency under the act or section 351 of the PHS Act who requests special protocol assessment.

2. Burden Estimate

Table 1 of this document provides an estimate of the annual reporting burden for requests for special protocol assessment. The procedures for requesting special protocol assessment that are set forth in the draft guidance have not been previously described by the agency, although the PDUFA goals and the requirements of section 505(b)(4)(B) of the act have been in effect since October and November 1998, respectively, as follows:

a. *Notification for a carcinogenicity protocol.* Based on data collected from the review divisions and offices within CDER and CBER, including the number of carcinogenicity protocols submitted for review in the first half of fiscal year (FY) 1999 and the number of IND's for new molecular entities that were received by the agency per year over the last 5 years, CDER and CBER anticipate that approximately 30 respondents will notify the agency of an intent to request special protocol assessment of a carcinogenicity protocol. The agency further estimates that the total annual responses, i.e., the total number of notifications that will be sent to CDER and CBER, will be 60, based on data collected from the offices within CDER and CBER. Therefore, the agency estimates that there will be approximately two responses per respondent. The hours per response, which is the estimated number of hours that a respondent would spend preparing the notification and background information to be submitted in accordance with the draft guidance, is estimated to be approximately 8 hours. While FDA has not finalized the separate guidance describing background information that should be submitted with notification of a carcinogenicity protocol for assessment, the agency anticipates that it will take respondents approximately 8 hours to gather and copy articles and study reports that are relevant to the carcinogenicity protocol. Therefore, the agency estimates that respondents will spend 480 hours per year notifying the agency of an intent to request special protocol assessment of a carcinogenicity protocol.

b. *Requests for special protocol assessment.* Based on data collected from the review divisions and offices within CDER and CBER, including the number of requests for special protocol assessment in the first half of FY 1999, the number of IND's for new molecular entities that were received by the agency per year over the past 5 years, the number of sponsors who have submitted protocols for agency review in the past and in the first half of FY 1999, and the number of end-of-phase 2/pre-phase 3 meetings that occur between respondents and the agency per year, FDA anticipates that 70 respondents will request special protocol assessment per year. The total annual responses are the total number of requests for special protocol assessment that are submitted to CDER and CBER in 1 year. Based on data collected from the review divisions and offices within CDER and CBER, FDA estimates that it will receive approximately 180 requests for special protocol assessment per year. Therefore, the agency estimates that there will be approximately 2.57 responses per respondent. The hours per response is the estimated number of hours that a respondent would spend preparing the information to be submitted with a request for special protocol assessment, including the time it takes to gather and copy questions to be posed to the agency regarding the protocol and data, assumptions, and information needed to permit an adequate evaluation of the protocol. Based on estimates provided by the regulated industry and on the agency's experience in requesting similar information, FDA estimates approximately 15 hours on average would be needed per response. Therefore, FDA estimates that 2,700 hours will be spent per year by respondents requesting special protocol assessment. Overall, FDA anticipates that respondents will spend 3,180 hours per year to participate in the programs described in the draft guidance.

FDA estimates the burden of this collection of information as follows:

TABLE 1.—ESTIMATED ANNUAL REPORTING BURDEN[1]

Notification and Requests	Number of Respondents	Number of Responses per Respondent	Total Annual Responses	Hours per Response	Total Hours
Notification for Carcinogenicity Protocols	30	2.0	60	8	480
Requests for Special Protocol Assessment	70	2.57	180	15	2,700
Total					3,180

[1]There are no capital costs or operating and maintenance costs associated with this collection of information.

Dated: 2/1/00
February 1, 2000

Jan Windsor

Margaret M. Dotzel
Acting Associate Commissioner for Policy

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